Journal of Translational Autoimmunity 9 (2024) 100247

Contents lists available at ScienceDirect

Journal of Translational Autoimmunity

journal homepage: www.sciencedirect.com/journal/journal-of-translational-autoimmunity

To switch or to swap? Evidence from a meta-analysis for the best treatment approach in childhood chronic uveitis resistant to the I anti-TNF

Ilaria Maccora [a,b,*], Sara Soldovieri [a], Teodoro Oliverio [a], Salvatore de Masi [c], Edoardo Marrani [a], Ilaria Pagnini [a], Maria Vincenza Mastrolia [a,b], Gabriele Simonini [a,b]

[a] Rheumatology Unit, ERN ReCONNET Centre, Meyer Children's Hospital IRCCS, Florence, Italy
[b] NeuroFARBA Department, University of Florence, Florence, Italy
[c] Clinical Trial Center, Careggi University Hospital, Florence, Italy

ARTICLE INFO

Handling Editor: Y Renaudineau

Keywords:
Uveitis
Children
Pediatric rheumatology
Anti-TNF
Anti-IL6
Anti-CTLA4
Jak-inhibitors
Adalimumab
Infliximab
Tocilizumab
Golimumab
Abatacept
Rituximab
Eye
Treatment
Therapy

ABSTRACT

Objective: Since adalimumab approval in childhood chronic non-infectious uveitis (cNIU), the prognosis has been dramatically changed, but the 25 % failed to achieve inactivity. There is not accordance if it is better to switch to another anti-TNF or to swap to another category of biologic. Thus, we aim to summarize evidence regarding the best treatment of cNIU refractory to the first anti-TNF.

Methods: A systematic literature review and meta-analysis, according to PRISMA Guidelines, was performed (Jan2000-Aug2023). Studies investigating the efficacy of treatment in cNIU refractory to the first anti-TNF were considered for inclusion. The primary outcome was the improvement of intraocular inflammation according to SUN. A combined estimation of the proportion of children responding to switch or swap and for each drug was performed.

Results: 23 articles were eligible, reporting 150 children of whom 109 switched anti-TNF (45 adalimumab, 49 infliximab, 9 golimumab) and 41 swapped to another biologics (31 abatacept, 8 tocilizumab and 1 rituximab). The proportion of responding children was 46 %(95 % CI 23-70) for switch and 38 %(95 % CI 8-73) for swap ($\chi^2$0.02, p = 0.86). Instead analysing for each drug, the proportion of responding children was the 24 %(95 % CI 2-55) for adalimumab, 43 %(95 % CI 2-80) for abatacept, 79 %(95 % CI 61-93) for infliximab, 56 %(95 % CI 14-95) for golimumab and 96 %(95 % CI 58-100) for tocilizumab. We evaluated a superiority of tocilizumab and infliximab compared to the other drugs(χ^2 27.5 p < 0.0001).

Conclusion: Although non-conclusive, this meta-analysis suggests that, after the first anti-TNF failure, tocilizumab and infliximab are the best available treatment for the management of cNIU.

Significance and innovation

- Little evidence are available regarding which treatment might be considered after the first anti-TNF failure in children with chronic non-infectious uveitis
- After adalimumab failure in childhood non-infectious uveitis, there are better chance to achieve ocular control if treated with tocilizumab and/or infliximab.
- This study results may contribute to update the current international recommendations regarding the management of pediatric uveitis.
- This study highlights existing gaps in the study reporting childhood non-infectious uveitis and randomised controlled trials for this disease.

1. Introduction

Childhood chronic non-infectious uveitis (cNIU) is a severe and disabling disease, posing a significant threat to eyesight, being able to lead to blindness [1–3]. Previous and recent international recommendations for the treatment of cNIU suggest a step-by-step approach with a progressive intensification of the immunosuppressive therapy [4,5]. There is agreement about the use of adalimumab, a biologic drug against

* Corresponding author. Rheumatology Unit, ERN ReConnet Center, Meyer Children's Hospital IRCCS, Florence, Italy, Viale Gaetano Pieraccini 24, 50139, Florence, Italy.
E-mail addresses: ilaria.maccora@unifi.it, ilamaccora@gmail.com (I. Maccora).

https://doi.org/10.1016/j.jtauto.2024.100247
Received 30 March 2024; Received in revised form 20 June 2024; Accepted 22 June 2024
Available online 22 June 2024

Tumour Necrosis Factor α (anti-TNFα), when a child fails to achieve inflammation control with conventional synthetic Disease modifying antirheumatic drugs (csDMARDs) or when severe complications are present at onset [4–6]. However, when the first anti-TNFα fails, there are not enough and solid evidence regarding which would be the best approach to treat these children.

Indeed, the awareness about the efficacy of adalimumab has been supported by the pivotal results of two randomized controlled trials (RCTs), the SYCAMORE and the ADJUVITE, and a recent meta-analysis about the use of anti-TNFα in cNIU [7–9]. Nevertheless, despite these strides, approximately 25 % of children with cNIU fail to respond to adalimumab [7–9].

Consequently, for those patients who fail the initial anti-TNFα, exploring alternative treatment strategies considering a non-anti-TNFα, of note to swap, or resorting to a second anti-TNFα, technically to switch using a drug belonging to the same family, may be warranted [9–13].

A recent single arm phase 2 trial by Ramanan et al. was recently published about the use of an anti-IL6, tocilizumab, in children resistant to other drugs [13]. It showed that 7/21 children treated with subcutaneous tocilizumab have an improvement of ocular inflammation, with good results especially in those with macular oedema. However, the trial did not meet the primary end-point and a phase III trial was not performed [13].

In this clinical context, several case series and observational studies report the off-label use of several other biologic drugs including others anti-TNFα as infliximab and golimumab (switch) as well as other classes of biologic as tocilizumab, or abatacept, a CTLA4 antagonist, or rituximab, an anti-CD20 (swap) [9,14–21].

Nevertheless, there is not clear evidence if it's better to switch to another anti-TNFα rather than to swap to another category of biologics. In 2014, a systematic review and meta-analysis tried to summarize such results, but they included only 40 patients with no comparator for the switch [11].

Therefore, there is a notable absence of recent systematic evaluation on this matter, that can provide a definitive guidance.

Thus, the aim of our study was to evaluate the effectiveness of switching to another anti-TNFα compared to swap to another class of biologic in cases of cNIU that did not respond to the first anti-TNFα treatment in a systematic literature review and meta-analysis.

2. Methods

According to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines (PRISMA), we performed a systematic literature review and meta-analysis to identify the existing evidence regarding the possible effectiveness of other biologic treatments when the first anti-TNFα fails in cNIU [22].

3. Search strategy and selection criteria

3.1. Search strategies

We performed a systematic literature search of the papers published between January 2000 and the 31st of August 2023 in EMBASE, PubMed/MEDLINE, and Evidence-Based Medicine with the following keywords: ("chronic uveitis" OR "chronic iridocyclitis" OR "recurrent uveitis" OR "refractory uveitis" OR "non-infectious uveitis" OR "autoimmune uveitis" OR "uveitis" OR "iridocyclitis") AND ("Abatacept" OR "Rituximab" OR "Tocilizumab" OR "Anakinra" OR " Canakinumab" OR "cytotoxic T-lymphocyte-associated antigen-4" OR " CTLA-4" OR "CD-20" OR "IL-1 receptor antagonist" OR "antagonist" OR "Anti-Il-6 receptor monoclonal antibody" OR "Anti-IL-6" OR "Anti-IL-1" OR "monoclonal antibodies" OR "biologics drugs" OR "Etanercept" OR "Infliximab" OR "Adalimumab" OR "Golimumab" OR "Anti-TNF-alpha" OR "TNF-alpha" OR "Anti-TNF-α" OR "Jak-inhibitors" OR "Baricitinib" OR "Tofacitinib"). We added a limitation excluding conference abstract. Of note, we did not include limitations regarding the age of patients in order to be able, when it was possible, to exclusively extract data of children from studies including adults and children together.

Title and abstract of the papers were screened independently by three reviewers (I.M., S.S. and T.O.) who excluded duplicates and obviously irrelevant papers. Then, full-text screening was performed by three independent reviewers (I.M., S.S. and T.O.) in order to determine which satisfied the eligibility criteria. When there was a disagreement, it was resolved through discussion with the senior author (G.S.). The references of all eligible articles including reviews, expert opinion papers and systematic reviews were manually searched for potentially eligible publications.

3.2. Eligibility criteria

Study were eligible if they reported data regarding patients: 1) with chronic non-infectious autoimmune uveitis according to the Standardization of Uveitis Nomenclature (SUN) criteria definition, that is persistent uveitis characterized by relapse within 3 months after discontinuation of therapy [23]; 2) have autoimmune uveitis refractory to a) topical and/or systemic steroid treatment, and/or at least one csDMARDs as methotrexate and/or azathioprine and/or cyclosporin and/or chlorambucil and/or mycophenolate mofetil) and b) a first course of a single anti-TNFα (as adalimumab, infliximab, etanercept, golimumab); c) the patients must not have received any other bDMARD before the first TNF inhibitor; 3) have disease onset at or before 16 years of age; 4) commencing the drug in study before 18 years old; 5) commencing one of the currently available biologic treatments for the management of active cNIU, after the first anti-TNFα treatment resulted a failure; 6) Observational studies. However, if the patients were receiving etanercept as first anti-TNFα, the subject was not considered eligible.

Additionally, to be eligible, the included studies required to report a) outcome measures that assessed the effectiveness of the treatment according to the SUN criteria for reporting clinical data or provided sufficient data from which we could extract this information [23]; b) to include a follow-up of at least a 6 (±2) months on treatment; c) to be in English language.

Exclusion criteria were: 1) starting time of the drug in study after 18 years of age; 2) lack of applicability to the SUN criteria definition of improvement in uveitis activity 2) individual case reports 3) papers where data were not extractable separately for children and adults; 4) papers where data were not extractable separately for children who received additional therapeutic lines; 5) single case reports, because their publication was likely importantly related to a positive outcome; 6) commencing the second biologic for other reasons than uveitis.

4. Data analysis

4.1. Data extractions

Data were extracted by a single reviewer (T.O. or S.S.) using a standard form and checked by a second reviewer (IM). The items extracted were the first author, the year of publication, the study design, the length of follow-up, characteristics of participants (number of children, sex, age and underlined disease), type of treatment (where switch means to start another anti-TNFα and swap means start another class of biologic as anti-IL6, or anti-CD20 etc), the specific drug started, previous treatment, and all outcome measures.

4.2. Outcome measures

The main outcome measure used to assess the effect of the treatment was the achievement of persistent intraocular inactivity according to the definition of the SUN working group criteria [23]. Anterior chamber inflammation was considered "inactive" or controlled if the

inflammatory activity was grading 0 cells for at least 6 months. The treatment was considered as successful, when the uveitis was inactive (grade 0) for at least at 6-month follow-up (±2). For studies not adherent to SUN criteria, we applied the SUN activity terminology with regard to reported activity grading, where possible, and only an activity grade of 0 was considered as improvement. If one eye improved, but the other eye worsened, the judgement was increased activity and the effect of treatment considered as failure.

As secondary outcomes, tapering and/or stopping systemic and topical steroid administration, improvement in visual acuity post treatment, time to persistent inactivity (the duration of treatment needed to achieve persistent inactivity), and safety of administered drug were also considered, when reported.

Regarding visual acuity outcomes, "normal" acuity was defined as at least a best-corrected visual acuity (BCVA) < 0.4 in a logMAR format. "Improved" visual acuity was defined as an improvement of visual acuity in at least 1 eye. The proportion of patients improved or stable in normal values at complete or nearly complete follow-up was considered the outcome of interest in visual acuity, according to the SUN working group criteria [23]. If these data were not extractable from the paper, the information was considered missing.

4.3. Statistical analysis

A meta-analysis was conducted to determine a combined estimate of proportion of children in eligible studies responding to the switch or to the swap and to each individual drug. Data on the number of patients responding positively to treatment and the total number of patients treated were extracted from each study, and a pooled effect estimate (the proportion of patients responding positively to treatment) was computed with a CI determined using the normal approximation method of the binomial CI. The effect measure for each study was the proportion of participants classified as responders on each therapy, with respect to intraocular inflammation [p(i)], where i refers to study i. If not provided in the original article, we calculated a 95 % CI for the observed proportion. We tested for heterogeneity between the effect estimates from studies by conducting Cochrane's v2 test, which has k 1 degrees of freedom, where k is the number of studies. In combining estimates, each study estimate was given a weight as the inverse of the proportion variance, i.e. n(i)/(p(i)[1 p(i)] for study i, where n(i) is the number of persons in study i. The combined estimate (p) and its standard error were then calculated in order to provide a 95 % CI for this combined estimate of the proportion of patients improving. Forest plots were created in Stata version 11 (StataCorp, College Station, TX, USA), using

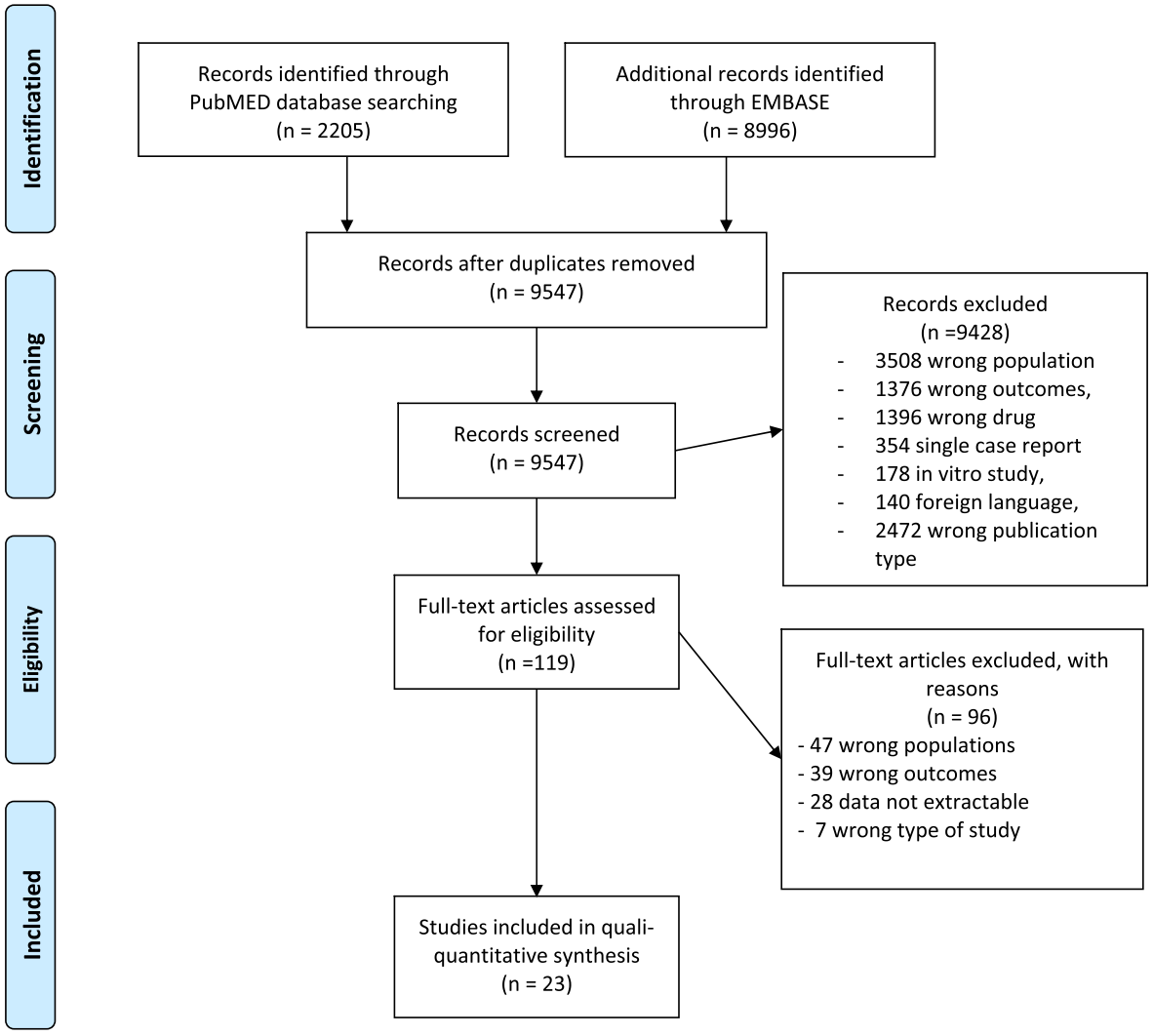

Fig. 1. Study flow diagram summarising the results of the literature search.
From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). *P*referred *R*eporting *I*tems for *S*ystematic Reviews and *M*eta-*A*nalyses: The PRISMA Statement. PLoS Med 6(7): e1000097. https://doi.org/10.1371/journal.pmed1000097
For more information, visit http://www.prisma-statement.org.

exact CIs with an a ¼ 0.05. However, where the proportion of responders was 0 % or 100 %, the variances of the raw proportions were stabilized using an arcsine transformation, using a random-effects mode.

The review protocol was not registered in Prospero.

5. Results

The search strategy identified 11,201 articles from the 1st of January 2000 to the 31st of July 2023. One thousand six hundred fifty-four articles were excluded because duplicates, and 9547 were screened for title and abstract. Of 9547 papers, 9428 were excluded for several different reasons: 3508 because reported only adult patients or animal models, 2472 because the type of publication as literature review or animal studies, 1396 reporting multiple drug changes or topical treatments or csDMARDs, 1376 not using the SUN criteria, 354 single case report, 178 in vitro study and 140 foreign language (Fig. 1). Of the remaining 119 papers, the full-text was assessed for inclusion, and 23 were included for the qualitative and quantitative synthesis (Fig. 1), while the others resulted not eligible according to the inclusion criteria, or data not-extractable and for study type. The phase II trial about the use of tocilizumab in children refractory to anti-TNFα in Juvenile Idiopathic arthritis associated uveitis was excluded because the different nature of the type of study [13].

Of these 23 papers, 11 articles reported data about the swap to another category of biologics other than anti-TNFα of treatment (9 abatacept, 1 rituximab and 3 tocilizumab) and 20 about the switch to another anti-TNFα (11 adalimumab, 4 golimumab, 7 infliximab) (see Tables 1 and 2) [15–20,24–40].

A total of 150 children were included in the analysis about the evaluation of switch or swap therapy and 143 about the analysis of each drug in 23 studies [15–20,24–40]. Seventy-six of these children were female and 24 were male, for the others the sex was not extractable. The number of children included for each study ranged from 1 to 14. Age at onset at the time of starting the new therapeutic line ranged from 2 to 16 years. Chronic uveitis was associated with JIA in 123 children (82 %), sarcoidosis in 1 (0.6 %), Behçet's disease in 3 (2 %), and idiopathic in 14 (9.3 %).

Most of the patients have an anterior uveitis (n = 95, 63.3 %), followed by panuveitis (n = 9,6 %), intermediate uveitis (n = 8, 5.3 %) and posterior uveitis (n = 2, 1.3 %) [15–20,24,25,27,29,30,32–34,36,37,39,40]. However, the data regarding the anatomical location of uveitis was not available or not extractable in 3 studies [26,35,38].

5.1. Intraocular inflammation improvement

All included studies assessed the response to treatment as anterior chamber cells or as appropriate based on the anatomical location, according to the definition of improvement of the SUN Working group criteria [23]. Data on 150 children from observational studies were analysed in a pooled analysis stratified as switch or swap therapy and 143 for each drug. The proportion of responding children was 46 % (95 % CI 23-70) for patients who switched from the first anti-TNF to another anti-TNF (53/109), and 38 % (95 % CI 8-73) for them who swap to another class of biologic drug (20/41), with no significant differences between the 2 groups ($\chi^2$0.02, p = 0.86) (see Fig. 2). In the group of switches, we try to identify if the previous treatment might predict the subsequent response to the switch and patients who switched from adalimumab to another anti-TNF had better chance to respond compared to children who switched from infliximab to another anti-TNF (41/71 vs 12/38, χ^2 6.78 p 0.008).

Stratifying the analysis by for each specific drug, the proportion of responding children was the 24 % (95 % CI 2-55) for adalimumab (12/45), 43 % (95 % CI 2-80) for abatacept (12/31), 79 % (95 % CI 61-93) for infliximab (36/49), 56 % (95 % CI 14-95) for golimumab (5/9), 96 % (95 % CI 58-100) for tocilizumab (7/8) and 100 % (95 % CI 0.21–1.00) for rituximab (1/1) (see Fig. 3). There was a clear difference in the pooled estimate response for patients for each drug (χ^2 27.5 p < 0.0001) with superiority of tocilizumab and infliximab compared to the other drugs. Conversely a direct comparison between tocilizumab and infliximab did not show a statistically significant difference (7/8 versus 36/49, $\chi^2$0.73 p 0.39).

There was evidence of heterogeneity across studies, overall (P < 0.001, I^2 58.48 %) and for the studies grouped by switch/swap (switch p < 0.001, swap 0.02) and for drug (adalimumab p 0.01, abatacept p 0.04, infliximab p 0.38, golimumab p 0.59).

Not all the secondary outcome variables were present in each study, or they were reported in different ways. Therefore, because of this relevant heterogeneity, we were not able to compute effect size analyses for these variables (Table 1).

5.2. Visual outcome

Among the 23 studies, the time to achieve persistent inactivity on treatment for each drug was reported in 7 studies, of whom 4 about abatacept with a range of 6–12 months, 2 about infliximab with a range of 8–20 months, 1 about golimumab in 9 months, and 1 about tocilizumab reporting 10 months [18,27–29,34,38,39].

Only 13 studies reported the variations about the visual acuity: 8 about abatacept (15/20 with normal visual acuity at the last available follow-up, 2/20 with stable visual acuity, 4/20 with improved visual acuity), 5 about adalimumab (6/18 with stable visual acuity, 6/18 with normal visual acuity, 3/18 with improved visual acuity, 1/18 with worsening of visual acuity), 3 about golimumab (6/8 with stable visual acuity, 1/8 with normal visual acuity, 1/8 with improved visual acuity), 1 about infliximab (3/6 with normal visual acuity), 1 about rituximab (1/1 with normal visual acuity) and 2 about tocilizumab (6/7 with normal visual acuity) [15,18,20,25–31,34,36,40].

5.3. Discontinuation of topical corticosteroid and tapering of corticosteroid

The discontinuation of topical corticosteroid was reported in 12 studies [15,17,24,27–30,33–35,40]. Based on the articles included, 12 of the 19 children treated with abatacept discontinued topical corticosteroid, 2 of the 21 treated with adalimumab, 8 of the 8 treated with golimumab, 6 of the 14 treated with infliximab and 1/1 of the children treated with tocilizumab.

While about the tapering of systemic corticosteroid the outcome was reported in 14 studies [15,17,24–27,29,31,33–36,39]. Nineteen of the 30 patients treated with abatacept, where the data was available, reduced/stopped systemic corticosteroids, 13 of the 20 treated with adalimumab, 4 of the 4 in golimumab, 22 of the 32 in infliximab, 1/1 in rituximab and 8/8 in tocilizumab.

5.4. Adverse event

Details about adverse events were reported in 5 studies: 2 about tocilizumab (2 injection reaction, 3 neutropenia and 1 increased transaminase), 1 about golimumab (CMV infection), 2 about abatacept (1 persistent diarrhea, 2 skin rash), 1 about infliximab (1 allergic reaction) (Table 1) [17,18,25,38,40].

6. Discussion

To the best of our knowledge this is the first meta-analysis that assessed which is the best available treatment when the first anti-TNFα failed to achieve ocular inactivity in cNIU in childhood. Because of the different nature of the studies, mainly retrospective studies and cases series, we excluded the phase II trial about the use of tocilizumab in JIA associated uveitis [13].

With this, we highlighted that the overall probability of improvement of intraocular inflammation in cNIU, who underwent to a

Table 1
summarizes the main findings of each paper by drug included in the present meta-analysis, in term of study type, number of patients included, and outcomes considered. List of abbreviations: JIA: juvenile idiopathic arthritis, m months, IFX infliximab, ADA adalimumab, ABA abatacept, TOC tocilizumab, MTX methotrexate, MMF mycophenolate mofetil, RTX rituximab, GOL golimumab, AZA Azathioprine, LEF leflunomide, CSA cyclosporine, N number, CCS corticosteroid, F-up follow-up, pts patients.

First Author and year of publication, study design	F-up (range) months	N of pts	N of pts for each disease	N of female	Median age at drug start (range), months	Median age at onset uveitis (range), months	Drug	Concomitant therapy	Uveitis activity (Descriptive)	N of pts who achieve remission	Time to achieve remission, months	N of pts with stable visual acuity	N of pts with normal visual acuity	N of pts with improved visual acuity	Worsening of Visual acuity	n of pts who reduced systemic ccs	N of pts who stopped local ccs	Duration of inactivity, Months	N of pts with relapse	Adverse event drug
Ashkenazy N et al., 2019, Retrospective	21 [8–31]	12	7 Idiopathic, 1 Sarcoidosis, 4 JIA	8	125 (96–192)		IFX	10 MTX 2 MMF	12 initial response to IFX	8/12	8,6 m [1–20]					8/12				none
Brambilla A et al., 2016, Case series	12	2	1 idiopathic, 1 JIA	1	Pediatric age	72–108	ABA	1/2 MTX	2 no response	0/2			2/2	2/2	0/2	2/2	2/2		0/2	–
Bravo-Ljubetic I et al., 2013, Retrospective study	109,5 (56-163)	2	1 JIA, 1 Idiopathic		87 [2–8,8–85,85–88]		ADA	1 MTX, 1 CyA	No response in 2 refractory uveitis despite ABA or IFX	0/2									1/2	
Breitbach M et al., 2016, Retrospective study		6	6 JIA			63,6	IFX		Secondary treatment failure to ADA	3/6			3/6			3/6				
		2	2 JIA			63,6	GOL		Secondary treatment failure to ADA	1/1			1/1			1/1				
		2	2 JIA			63,6	ABA		Secondary treatment failure to ADA	1/2			1/2			1/2				
		3	3 JIA			63,6	TOC		Secondary treatment failure to ADA	2/3			2/3			2/3				
		1	1 JIA			63,6	RTX		Secondary treatment failure to ADA	1/1			1/1			1/1				
Dhingra M et al., 2009, Case series	7 [6–9]	4	3 JIA, 1 Idiopathic	3	90 (24–156)		ADA	1 MTX, 3 MMF	4 Persistent uveitis despite IFX	2/4		3/4	1/4			2/4		6		
Dipasquale V et al., 2019, Case series	90 (48–132)	1	2 JIA	1	150 (144–156)	66 (36–96)	TOC	1 MTX	for recurrent relapse	1/1						2/2	2/2	33	0/2	1 injection site reaction
	132	1	1 JIA	1	96	36	ADA	1 MTX	1 recurrence despite IFX	1/1						1/1		48	1/1	
Doycheva D et al., 2014, Retrospective study		3					IFX		Switch from ADA for scarse response	3/3										
Elhai M et al., 2011, Letter case series	16	1	1 JIA	1	132	36	ABA		1 relapse despite anti TFN	1/1	2	1/1	1/1	0/1	0/2		1/2	14		none
	10	1	1 JIA	1	84	36	IFX		Inefficacy of ADA	0/1										
Heiligenhaus A et al., 2011 Retrospective study	11 [7–18]	3	3 JIA	4	180 (168–180)	36 [36–48]	ADA		3 no response	0/4										
Interlandi E et al., 2014, Retrospective study		2	2 Behçet	0	104–204	96–180	ADA	2 AZA	2 control	2/2		1/2	0/2	1/2	0/2	2/2				none
Kenawy N et al., 2010, Case series	12	2	2 JIA	2	180		ABA		Response with ABA	2/2	6		1/2	2/2		2/2	2/2	12	0/2	
Lanz S et al., 2021, Retrospective study	25.2 (6–66)	8	8 JIA	6			GOL	4/6; MTX [3], AZA [1]	4/5 Initial response, then loss of response; 1/5 primary non-responder	3/5		5/5					6/6		1/6	1 infection (CMV HHV)

(*continued on next page*)

Table 1 (*continued*)

First Author and year of publication, study design	F-up (range) months	N of pts	N of pts for each disease	N of female	Median age at drug start (range), months	Median age at onset uveitis (range), months	Drug	Concomitant therapy	Uveitis activity (Descriptive)	N of pts who achieve remission	Time to achieve remission, months	N of pts with stable visual acuity	N of pts with normal visual acuity	N of pts with improved visual acuity	Worsening of Visual acuity	n of pts who reduced systemic ccs	N of pts who stopped local ccs	Duration of inactivity, Months	N of pts with relapse	Adverse event drug
	25.2 (6–66)	2	2 JIA	2			ADA	2 MTX	2/2 partial response to INX treatment	0/2		2/2								
Maccora I et al., 2022, Retrospective study	22.5 (3–97)	4	2 JIA, 1 Behçet, 1 idiopathic	2	118 m (65-191)	30 m (12-105)	TOC		4 Initial response	4/4	10.8		4/4			4/4			0/8	3 neutropenia, 1 infection, 1 increased transaminase
		1	1 JIA	1	113.5	63	GOL	1 MTX	No response	0/1			1/1			3/5		22,5	2/5	
	22.5 (6–97)	9	9 JIA	8	113.5 (35–151)	29 (20–83)	ABA		8 Initial response, 5 remission	5/9	11.8		9/9			3/5		22,5	2/5	1 persistent diarrhea, 1 dermatological rash
Marrani E et al., 2015, Case series	36	2	2 idiopathic	1	174	104	ABA	2 MTX	Relapsing during IFX and ADA	2/2	8,5		1/2			2/2	2/2		0/2	
Mesquida M et al., 2017, Retrospective Study	24	1	1 JIA	1			ADA		Persistent uveitis-related Macular-aedema despite treatment INX	0/1										
Miraldi Utz et al., 2019, Retrospective study	41,6	14	14 JIA				IFX		Failure of ADA treatment	12/14						11/12	6/12			
Roberts JE et al., 2022, Retrospective study	24	12			132	76	IFX		9 achieve remission, 2 uncontrolled uveitis, 1 stopped for Aes	9/12	3							24		allergic reaction
Salek SS et al., 2018, Case series	97 (51–143)	3	3 JIA	2		81 (36–144)	ADA	3 MTX	2 response remission, 1 failed ada and switched to ustekinumab	2/3										
	97 (51–143)	1	1 idiopathic	0		81 (36–144)	IFX	1 MTX	1 No response, switch to toc	0/1										
Sen ES et al., 2012, Retrospective study	24 [6–36]	6	6 JIA	5			ADA	5 MTX, 3 MMF	5 response, 1 relapse	4/6			5/6	2/6	1/6		1/6		1/6	
Tappeiner C et al., 2015, Retrospective study	12	11	21 JIA	6	141.6	51.6	ABA	10 MTX, 1 CSA		1/11						3/21	3/21		8/11	–
Tynjala P et al., 2008, Retrospective study	12	15	15 JIA	13	160.8	56.4 (15.6–166.8)	ADA	11 MTX, 4 LEF, 1 AZA, 5 CSA	7 response, 1 worsening	1/15						7/15	1/15			
William M et al., 2012, Case series	18	1	1 JIA	1			ABA	1 MTX	No response	0/1		1/1				2/2	2/2	12	0/2	
	18	1	1 JIA	1			GOL	1 MTX	1 initial response and remission	1/1	3	1/1		1/1		2/2	2/2	12	0/2	
Zulian F et al., 2010, Retrospective study	9.2 [7–11]	1	1 JIA	1			ABA	1 MTX	1 initial response	0/1		1/1			3/6	4/4			2/6	1 Rash
	9.2 [7–11]	5	5 JIA	4		73.2 (36–168)	ADA	5 MTX	0 Remission	0/5										

Table 2
Reports the main findings for each paper based on the switch or the swap to another drug, reporting the main outcomes considered in our meta-analysis. List of abbreviations: N number, pts patients, CCS corticosteroid.

First Author, year	Journal	Drug	N of pts in drug	N of pts who achieve remission	Time to achieve persistent inactivity, months	N of pts with stable visual acuity	N of pts with improved visual acuity	N of pts with normal visual Acuity	Worsening of Visual acuity	n of pts who reduced systemic ccs	N of pts who stopped local ccs
Ashkenazy N et al., 2019	Journal of AAPOS	SWITCH	12	8/12	8,6					8/12	
Brambilla A et al., 2016	The Journal of Rheumatology	SWAP	2	0/2			2/2	2/2	0/2	2/2	2/2
Bravo-Ljubetic I, 2013	Journal of AAPOS	SWAP	1	0/1							
	Journal of AAPOS	SWITCH	1	0/1							
Breitbach M et al., 2016	Graefe's Archive for Clinical and Experimental Ophthalmology	SWITCH	7	4/7			4/7			4/7	
	Graefe's Archive for Clinical and Experimental Ophthalmology	SWAP	6	4/6			4/6			4/6	
Dhingra M et al., 2009	Eye	SWITCH	4	2/4		3/4	1/4			2/4	
Dipasquale v. et al., 2019	Journal Clin Pharm Ther	SWAP	1	1/1						1/1	1/1
	Journal Clin Pharm Ther	SWITCH	1	1/1						1/1	
Doycheva D et al., 2014	Br J Ophthalmol	SWITCH	3	3/3							
Elhai M et al., 2011	Arthritis Care & Research	SWAP	1	1/1	2		1/1				1/1
	Arthritis Care & Research	SWITCH	1	1/1							
Heiligenhaus A 2011	Rheumathology	SWITCH	4	0/4							
Interlandi E et al., 2014	Clin & Experimental Rheumatology	SWITCH	2	2/2		1/2	1/2	0/2	1/2	2/2	
Kenawy N et al., 2010	Graefes Archive for Clinical and Experimental Ophthalmology	SWAP	2	2/2	2		1/2	2/2	0/2	2/2	
Lanz S et al., 2021	Pediatric Rheumatology	SWITCH	7	3/7		7/7					
Maccora I et al., 2022	Frontiers in Pediatrics	SWITCH	1	0/1							
	Frontiers in Pediatrics	SWAP	13	9/13	10.8			13/13		13/13	
Marrani E et al., 2015	Graefes Archive for Clinical and Experimental Ophthalmology	SWAP	2	2/2	8,5		1/2			2/2	2/2
Mesquida M et al., 2017	Retina	SWITCH	1	0/1							
Miraldi Utz et al., 2019	Pediatric Rheumatology	SWITCH	14	12/14						11/12	6/12
Roberts JE et al., 2022	J Clin Rheumatology	SWITCH	12	9/12	3						
Salek SS et al., 2018	Am J Ophthalmol	SWITCH	4	2/4			2/4		2/4		
Sen ES et al., 2012	Rheumatology	SWITCH	6	4/6			5/6	2/6	1/6		1/6
Tappeiner C et al., 2015	The Journal of Rheumatology	SWAP	11	1/11						3/21	3/21
	The Journal of Rheumatology	SWITCH	8	0/8							
Tynjala P et al., 2008	Rheumatology	SWITCH	15	1/15						7/15	1/15
William M et al., 2012	J Ophthal Inflamm Infect	SWAP	1	0/1	3					1/1	1/1
	J Ophthal Inflamm Infect	SWITCH	1	1/1	3	1/1		1/1		1/1	1/1
Zulian F et al., 2010	Arthritis Care & Research	SWAP	1	0/1							
	Arthritis Care & Research	SWITCH	5	0/5							

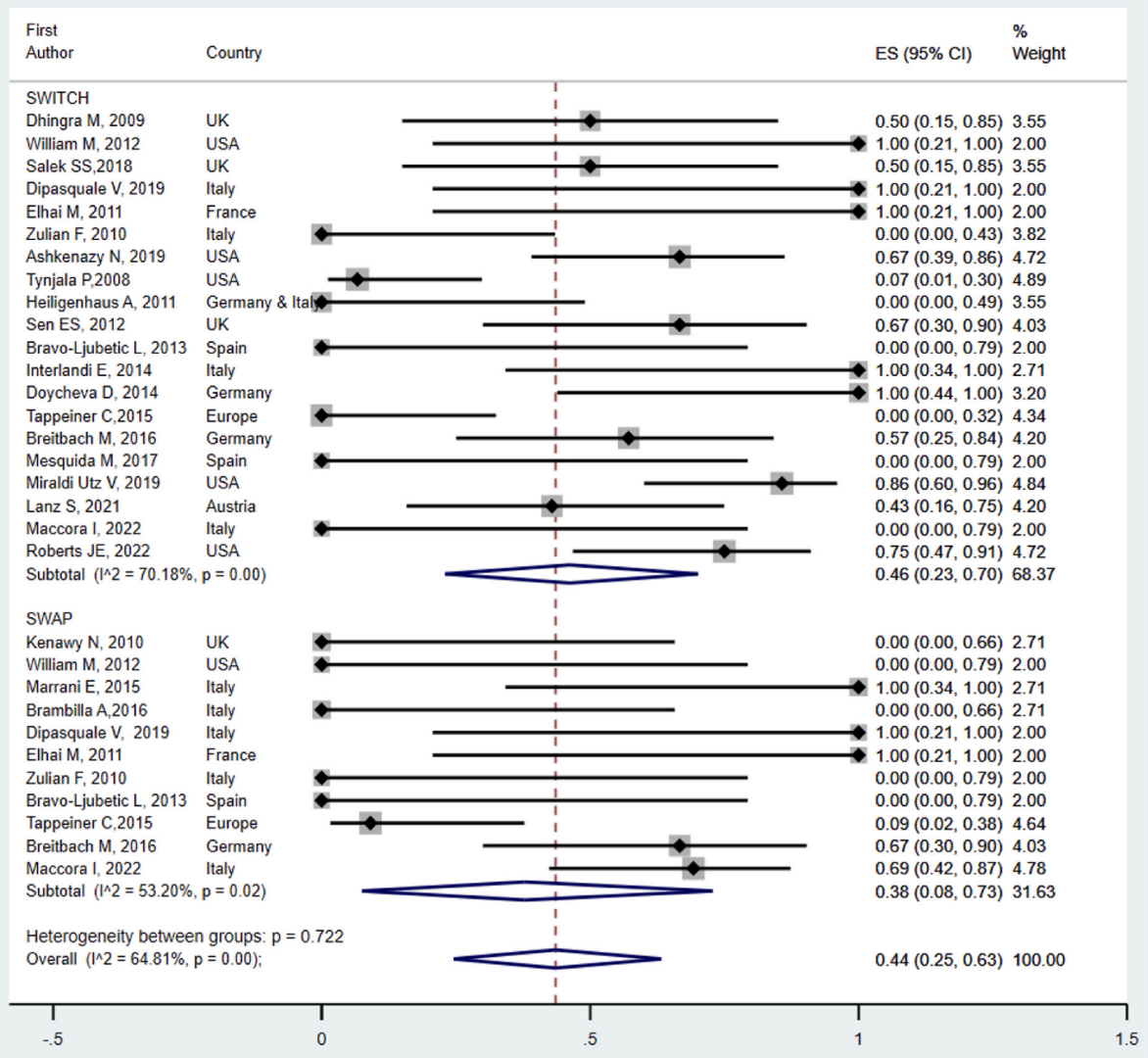

Fig. 2. Forest plot reporting using random effects meta-analysis of response to treatment differences according to SUN by switch and swap.

therapeutic switch and to a therapeutic swap was 46 % and 38 % respectively, with no significant differences between the two modalities. However, comparing each drug included in the study we were able to identify a significant superiority of tocilizumab and infliximab compared to other drugs, but with no difference between them. Moreover, we identified that switching from adalimumab to another anti-TNF, such as infliximab, is a meaningful alternative to consider. However, this is not the case when the child switches from infliximab to another anti-TNF.

These data support the most recent recommendations about the management of childhood cNIU suggest two possible different approaches [4,41]. In particular the European, provided by the Multinational Interdisciplinary Working Group for Uveitis in Childhood (MIWGUC) group are extremely in line with these findings highlighting that one the first anti-TNFα, generally adalimumab, one may switch to infliximab or tocilizumab [4]. While the American recommendations by the American College of Rheumatology suggest to switch to a second anti-TNFα before change class of biologic [41]. However, this last were published in 2019 and might reflect of a more limited presence of evidence.

Indeed, several papers were published in the last 5–8 years about the use of non-anti-TNFα in childhood cNIU, and only a few directly compared the two possible approaches or/and the different drugs.

In 2014, a systematic literature review about the use of non-anti-TNFα biologic in cNIU was published by our group [12]. However, this meta-analysis included the data of only 12 children that were treated with rituximab, abatacept and tocilizumab after several drugs changes [12]. Nonetheless they were able to show that non-anti-TNFα are a valid choice in case of anti-TNFα failure.

Most recently, another retrospective study tried to identify which could be the best treatment between tocilizumab and abatacept and they showed the better effectiveness of tocilizumab in this clinical context [18]. However not all the patients were immediately treated with one of these drugs after anti-TNFα failure.

Moreover, another recent paper by Kreps et al. compared the effectiveness of infliximab to another class of biologic when children with cNIU failed to achieve inflammation control with adalimumab [42]. However, we were not able to include this specific study in our meta-analysis because it did not fulfil our inclusion criteria, specifically several patients received infliximab after several course of different drugs and the data were not extractable for single patients. In this specific setting they highlighted the effectiveness of infliximab in these children, but they were not able to perform a direct comparison with other biologics because of the limited number of patients included in the second group (only 5)[42].These results seem to be partially in line with our results, but they were not able to address our specific questions if it is better to switch to another anti-TNFα after failing the first one, or to swap to another class of biologics.

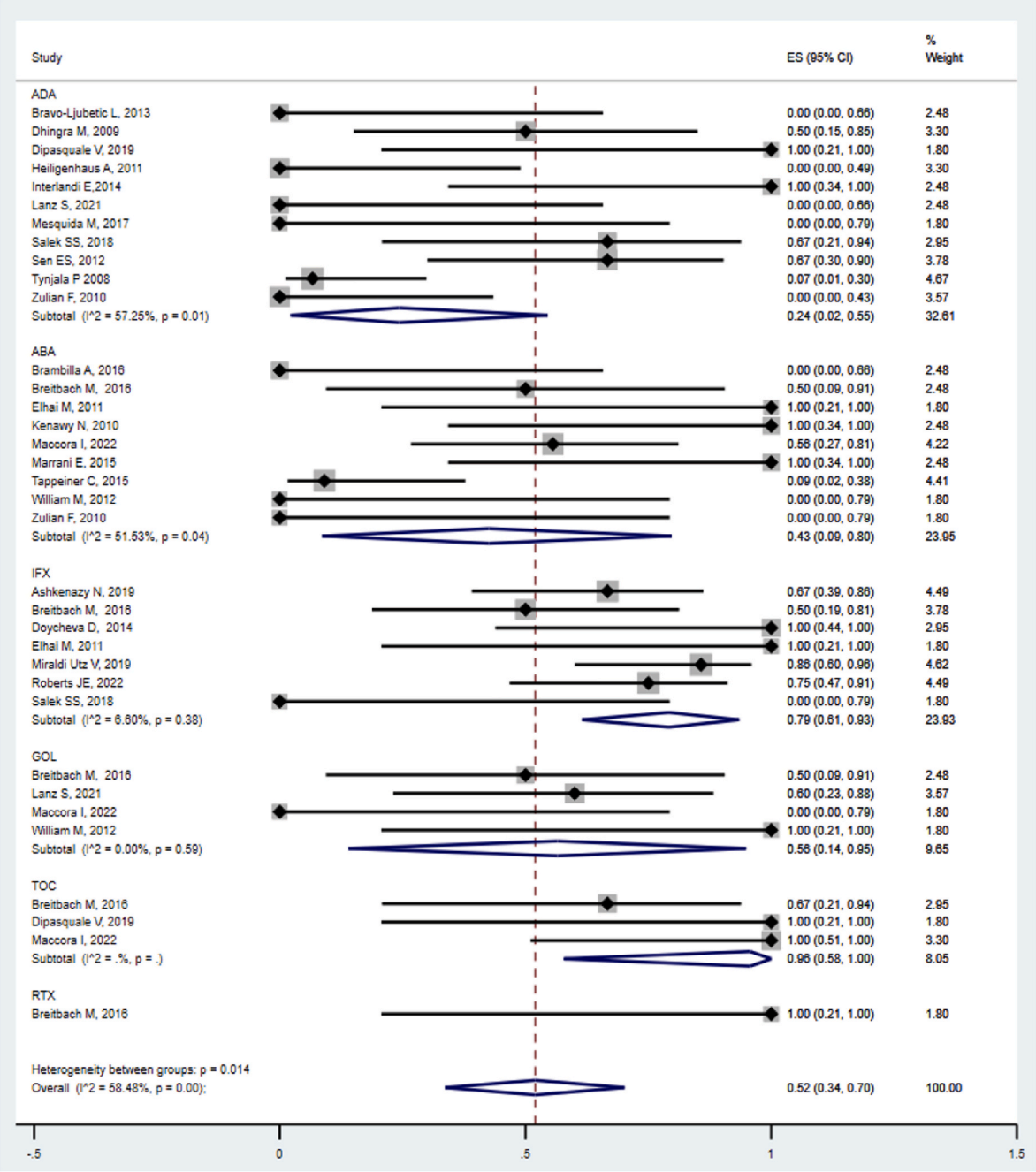

Fig. 3. Forest plot reporting using random effects meta-analysis of response to treatment differences according to SUN by drug.

Our results about tocilizumab and infliximab seem in agreement with recent literature, that we were not able to include in our meta-analysis because the children treated with these drugs received several biologics before the specific drug in study [19,21,43–45].

Intriguingly, all the children included in our meta-analysis treated with tocilizumab received the drug intravenously every four weeks with excellent results. However, contrasting data come from the literature, regarding the effectiveness of tocilizumab when administered subcutaneously. Indeed the phase II trial by Ramanan et al. assessed the effectiveness of this drug subcutaneously and not intravenously, showing that only one third of the children treated achieved inflammation control [13]. However, a recent study by Burlo et al. showed that also this formulation of tocilizumab is able to lead to persistent inactivity in the 60 % of children with anti-TNFα resistant uveitis [46].

Regarding secondary outcomes the data were not reported in a consistent way in the different studies, making the comparison extremely difficult. However, the data regarding the safety of these drugs are extremely reassuring and in line with data from other paediatric use [17,18,25,38,40,47–49].

Additionally, the data regarding the corticosteroid discontinuation (topical and systemic) and visual acuity clearly reflect the effectiveness of the drug in study. However based on our literature review, all the drugs were able to lead the maintaining of normal visual acuity, at least for those patients where this specific outcome was reported [18,27–29,34,38,39].

Before drawing our conclusion, we need to discuss several caveats and limitations.

Firstly, in the present study, most of the included patients have JIA associated uveitis and an anterior subtype of uveitis, which is not completely representative of all types of cNIU, although JIA represents

the leading cause in childhood. The percentage and distribution of the different aetiologies of the enrolled cNIUs clearly represents the epidemiology of cNIU. Additionally, because of our inclusion criteria and our aim to assess which is the best available treatment after the failure of the first anti-TNFα, we were able to include only 23 papers, excluding several studies that report data regarding not-anti-TNFα biologic (swap) after they received more than 1 biologics because of a previous switch or swap [14,19,29,33,35,44–46,50,51]. However, this inclusion selection criteria made the population homogenous and the comparisons generalizable to a greater similar overall population. Additionally, this inclusion criteria have led to a low number of patients with complete data for the second biologic, specifically for non-infliximab and non-tocilizumab biologic.

We excluded papers which reported the effectiveness of switch or swap/or of the specific drug, in adults who presents a childhood onset of cNIU as our aim was to estimate the effect-size of the switch versus the swap at the time of childhood and provide consistent data for this clinical query at this time of age.

The role of Janus Kinase Inhibitors (JAKi) has not been explored, as the current available data belongs to adult patients with non-infectious uveitis [52]. An ongoing clinical trials in children about the use of this class of drug in Europe will soon provide additional data [52].

A comparative analysis of the secondary outcomes among the different groups was not possible as most of the papers did not provide this datum in a consistent way.

As the nature/rarity of the disease, the number of studies and their quality, mainly retrospective studies and case series resulted, hampered the chance to perform an evaluation of the quality of the studies.

In conclusion, according this meta-analysis, there is no difference between switching and swapping in cNIU treatment after the failure of the first anti-TNFa, of note adalimumab. However, there is evidence of superiority of infliximab and tocilizumab compared to other drugs used up to know. According to the Oxford Centre for Evidence-based Medicine Levels of Evidence, these results reach an evidence level of 2 [53].

Further prospective comparative studies, that directly addresses our specific aims, are needed to clearly highlight which is the best available treatment after adalimumab failure in childhood cNIU.

Funding

None.

Data sharing

Completed data that support the findings of this study are available on reasonable request from the corresponding author Ilaria Maccora at ilaria.maccora@unifi.it.

CRediT authorship contribution statement

Ilaria Maccora: Writing – review & editing, Writing – original draft, Validation, Supervision, Methodology, Investigation, Formal analysis, Data curation, Conceptualization. **Sara Soldovieri:** Writing – original draft, Investigation, Data curation. **Teodoro Oliverio:** Investigation, Data curation. **Salvatore de Masi:** Writing – review & editing, Supervision, Formal analysis. **Edoardo Marrani:** Writing – review & editing, Conceptualization. **Ilaria Pagnini:** Writing – review & editing. **Maria Vincenza Mastrolia:** Writing – review & editing. **Gabriele Simonini:** Writing – review & editing, Supervision, Methodology, Formal analysis, Conceptualization.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data availability

Data will be made available on request.

Acknowledgments

This work was supported, in part, by funds from the 'Current Research Annual Funding' of the Italian Ministry of Health

References

[1] I. Maccora, C. Guly, C de Libero, R. Caputo, A.V. Ramanan, G. Simonini, Childhood chronic idiopathic uveitis in a multicentre international cohort, Ocul. Immunol. Inflamm. (2023) 1–10, https://doi.org/10.1080/09273948.2023.2169715.
[2] I. Maccora, E.S. Sen, A.V. Ramanan, Update on noninfectious uveitis in children and its treatment, Curr. Opin. Rheumatol. 32 (2020) 395–402, https://doi.org/10.1097/BOR.0000000000000723.
[3] I. Maccora, E. Marrani, I. Pagnini, et al., Challenges and management of childhood noninfectious chronic uveitis, Expet Rev. Clin. Immunol. 19 (2023) 599–611, https://doi.org/10.1080/1744666X.2023.2198210.
[4] I. Foeldvari, I. Maccora, H. Petrushkin, et al., New and updated recommendations for the treatment of juvenile idiopathic arthritis-associated uveitis and idiopathic chronic anterior uveitis, Arthritis Care Res. 75 (2023) 975–982, https://doi.org/10.1002/acr.24963.
[5] T. Constantin, I. Foeldvari, J. Anton, et al., Consensus-based recommendations for the management of uveitis associated with juvenile idiopathic arthritis: the SHARE initiative, Ann. Rheum. Dis. 77 (2018) 1107–1117, https://doi.org/10.1136/annrheumdis-2018-213131.
[6] A. Heiligenhaus, K. Minden, C. Tappeiner, et al., Update of the evidence based, interdisciplinary guideline for anti-inflammatory treatment of uveitis associated with juvenile idiopathic arthritis, Semin. Arthritis Rheum. 49 (2019) 43–55, https://doi.org/10.1016/j.semarthrit.2018.11.004.
[7] A.V. Ramanan, A.D. Dick, A.P. Jones, et al., Adalimumab plus methotrexate for uveitis in juvenile idiopathic arthritis, N. Engl. J. Med. 376 (2017) 1637–1646, https://doi.org/10.1056/NEJMoa1614160.
[8] P. Quartier, A. Baptiste, V. Despert, et al., ADJUVITE: a double-blind, randomised, placebo-controlled trial of adalimumab in early onset, chronic, juvenile idiopathic arthritis-associated anterior uveitis, Ann. Rheum. Dis. 77 (2018) 1003–1011, https://doi.org/10.1136/annrheumdis-2017-212089.
[9] I. Maccora, E. Fusco, E. Marrani, A.V. Ramanan, G. Simonini, Changing evidence over time: updated meta-analysis regarding anti-TNF efficacy in childhood chronic uveitis, Rheumatology (Oxford) 60 (2021) 568–587, https://doi.org/10.1093/rheumatology/keaa595.
[10] G. Simonini, A. Taddio, M. Cattalini, et al., Prevention of flare recurrences in childhood-refractory chronic uveitis: an open-label comparative study of adalimumab versus infliximab, Arthritis Care Res. 63 (2011) 612–618, https://doi.org/10.1002/acr.20404.
[11] G. Simonini, D. Katie, R. Cimaz, G.J. Macfarlane, G.T. Jones, Does switching anti-TNFα biologic agents represent an effective option in childhood chronic uveitis: the evidence from a systematic review and meta-analysis approach, Semin. Arthritis Rheum. 44 (2014) 39–46, https://doi.org/10.1016/j.semarthrit.2014.03.001.
[12] G. Simonini, R. Cimaz, G.T. Jones, G.J. Macfarlane, Non-anti-TNF biologic modifier drugs in non-infectious refractory chronic uveitis: the current evidence from a systematic review, Semin. Arthritis Rheum. 45 (2015) 238–250, https://doi.org/10.1016/j.semarthrit.2015.05.006.
[13] A.V. Ramanan, A.D. Dick, C. Guly, et al., Tocilizumab in patients with anti-TNF refractory juvenile idiopathic arthritis-associated uveitis (APTITUDE): a multicentre, single-arm, phase 2 trial, Lancet Rheumatol 2 (2020) e135–e141, https://doi.org/10.1016/S2665-9913(20)30008-4.
[14] C. Birolo, M.E. Zannin, S. Arsenyeva, et al., Comparable efficacy of abatacept used as first-line or second-line biological agent for severe juvenile idiopathic arthritis-related uveitis, J. Rheumatol. 43 (2016) 2068–2073, https://doi.org/10.3899/jrheum.151389.
[15] A. Brambilla, R. Caputo, R. Cimaz, G. Simonini, Canakinumab for childhood sight-threatening refractory uveitis: a case series, J. Rheumatol. 43 (2016) 1445–1447, https://doi.org/10.3899/jrheum.160064.
[16] L. Bravo-Ljubetic, J. Peralta-Calvo, S. Noval, N. Pastora-Salvador, J. Abelairas-Gómez, R. Merino, Adalimumab therapy for refractory childhood uveitis, J AAPOS 17 (2013) 456–459, https://doi.org/10.1016/j.jaapos.2013.06.009.
[17] V. Dipasquale, M. Atteritano, J. Fresta, I. Castagna, G. Conti, Tocilizumab for refractory uveitis associated with juvenile idiopathic arthritis: a report of two cases, J. Clin. Pharm. Therapeut. 44 (2019) 482–485, https://doi.org/10.1111/jcpt.12821.
[18] I. Maccora, S. Abu Rumeileh, F. Curci, et al., Tocilizumab and abatacept for the treatment of childhood chronic uveitis: a monocentric comparison experience, Front Pediatr 10 (2022) 851453, https://doi.org/10.3389/fped.2022.851453.
[19] M. Mesquida, B. Molins, V. Llorenç, et al., TWENTY-FOUR month follow-up of tocilizumab therapy for refractory uveitis-related macular EDEMA, Retina 38 (2018) 1361–1370, https://doi.org/10.1097/IAE.0000000000001690.
[20] A. Heiligenhaus, E. Miserocchi, C. Heinz, V. Gerloni, K. Kotaniemi, Treatment of severe uveitis associated with juvenile idiopathic arthritis with anti-CD20 monoclonal antibody (rituximab), Rheumatology (Oxford) 50 (2011) 1390–1394, https://doi.org/10.1093/rheumatology/ker107.

[21] M.E. Zannin, C. Birolo, V.M. Gerloni, et al., Safety and efficacy of infliximab and adalimumab for refractory uveitis in juvenile idiopathic arthritis: 1-year followup data from the Italian Registry, J. Rheumatol. 40 (2013) 74–79, https://doi.org/10.3899/jrheum.120583.
[22] D. Moher, L. Shamseer, M. Clarke, et al., Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015 statement, Syst. Rev. 4 (2015) 1, https://doi.org/10.1186/2046-4053-4-1.
[23] D.A. Jabs, R.B. Nussenblatt, J.T. Rosenbaum, Standardization of uveitis nomenclature for reporting clinical data. Results of the First International Workshop, Am. J. Ophthalmol. 140 (2005) 509–516, https://doi.org/10.1016/j.ajo.2005.03.057.
[24] P. Tynjälä, K. Kotaniemi, P. Lindahl, et al., Adalimumab in juvenile idiopathic arthritis-associated chronic anterior uveitis, Rheumatology (Oxford) 47 (2008) 339–344, https://doi.org/10.1093/rheumatology/kem356.
[25] F. Zulian, M. Balzarin, F. Falcini, et al., Abatacept for severe anti-tumor necrosis factor alpha refractory juvenile idiopathic arthritis-related uveitis, Arthritis Care Res. 62 (2010) 821–825, https://doi.org/10.1002/acr.20115.
[26] N. Dhingra, J. Morgan, A.D. Dick, Switching biologic agents for uveitis, Eye 23 (2009) 1868–1870, https://doi.org/10.1038/eye.2009.203.
[27] N. Kenawy, G. Cleary, D. Mewar, N. Beare, A. Chandna, I. Pearce, Abatacept: a potential therapy in refractory cases of juvenile idiopathic arthritis-associated uveitis, Graefes Arch. Clin. Exp. Ophthalmol. 249 (2011) 297–300, https://doi.org/10.1007/s00417-010-1523-6.
[28] M. Elhai, C.J. Deslandre, A. Kahan, Abatacept for refractory juvenile idiopathic arthritis-associated uveitis: two new cases. Comment on the article by Zulian et al, Arthritis Care Res. 63 (2011) 307–308, https://doi.org/10.1002/acr.20359, author reply 308.
[29] M. William, S. Faez, G.N. Papaliodis, A.-M. Lobo, Golimumab for the treatment of refractory juvenile idiopathic arthritis-associated uveitis, J Ophthalmic Inflamm Infect 2 (2012) 231–233, https://doi.org/10.1007/s12348-012-0081-y.
[30] E.S. Sen, S. Sharma, A. Hinchcliffe, A.D. Dick, A.V. Ramanan, Use of adalimumab in refractory non-infectious childhood chronic uveitis: efficacy in ocular disease–a case cohort interventional study, Rheumatology (Oxford) 51 (2012) 2199–2203, https://doi.org/10.1093/rheumatology/kes212.
[31] E. Interlandi, P. Leccese, I. Olivieri, L. Latanza, Adalimumab for treatment of severe Behçet's uveitis: a retrospective long-term follow-up study, Clin. Exp. Rheumatol. 32 (2014) S58–S62.
[32] D. Doycheva, M. Zierhut, G. Blumenstock, et al., Immunomodulatory therapy with tumour necrosis factor α inhibitors in children with antinuclear antibody-associated chronic anterior uveitis: long-term results, Br. J. Ophthalmol. 98 (2014) 523–528, https://doi.org/10.1136/bjophthalmol-2013-303935.
[33] C. Tappeiner, E. Miserocchi, B. Bodaghi, et al., Abatacept in the treatment of severe, longstanding, and refractory uveitis associated with juvenile idiopathic arthritis, J. Rheumatol. 42 (2015) 706–711, https://doi.org/10.3899/jrheum.140410.
[34] E. Marrani, V. Paganelli, C de Libero, R. Cimaz, G. Simonini, Long-term efficacy of abatacept in pediatric patients with idiopathic uveitis: a case series, Graefes Arch. Clin. Exp. Ophthalmol. 253 (2015) 1813–1816, https://doi.org/10.1007/s00417-015-3140-x.
[35] V. Miraldi Utz, S. Bulas, S. Lopper, et al., Effectiveness of long-term infliximab use and impact of treatment adherence on disease control in refractory, non-infectious pediatric uveitis, Pediatr Rheumatol Online J 17 (2019) 79, https://doi.org/10.1186/s12969-019-0383-9.
[36] M. Breitbach, C. Tappeiner, M.R.R. Böhm, et al., Discontinuation of long-term adalimumab treatment in patients with juvenile idiopathic arthritis-associated uveitis, Graefes Arch. Clin. Exp. Ophthalmol. 255 (2017) 171–177, https://doi.org/10.1007/s00417-016-3497-5.
[37] S.S. Salek, A. Pradeep, C. Guly, A.V. Ramanan, J.T. Rosenbaum, Uveitis and juvenile psoriatic arthritis or psoriasis, Am. J. Ophthalmol. 185 (2018) 68–74, https://doi.org/10.1016/j.ajo.2017.10.018.
[38] J.E. Roberts, P.A. Nigrovic, M.S. Lo, M.H. Chang, Weekly adalimumab, an effective alternative for refractory uveitis in children, J. Clin. Rheumatol. 28 (2022) e301–e304, https://doi.org/10.1097/RHU.0000000000001707.
[39] N. Ashkenazy, U.S. Saboo, A. Abraham, C. Ronconi, J.H. Cao, Successful treatment with infliximab after adalimumab failure in pediatric noninfectious uveitis, J AAPOS 23 (2019) 151.e1–151.e5, https://doi.org/10.1016/j.jaapos.2019.02.006.
[40] S. Lanz, G. Seidel, A. Skrabl-Baumgartner, Golimumab in juvenile idiopathic arthritis-associated uveitis unresponsive to Adalimumab, Pediatr Rheumatol Online J 19 (2021) 132, https://doi.org/10.1186/s12969-021-00630-1.
[41] S.T. Angeles-Han, S. Ringold, T. Beukelman, et al., American College of rheumatology/arthritis foundation guideline for the screening, monitoring, and treatment of juvenile idiopathic arthritis-associated uveitis, Arthritis Care Res. 71 (2019) 703–716, https://doi.org/10.1002/acr.23871, 2019.
[42] E.O. Kreps, S.J. Epps, A. Consejo, A.D. Dick, C.M. Guly, A.V. Ramanan, Infliximab in chronic non-infectious paediatric uveitis refractory to previous biologic therapy, Eye (2023), https://doi.org/10.1038/s41433-023-02795-3.
[43] G. Simonini, A. Taddio, M. Cattalini, et al., Superior efficacy of Adalimumab in treating childhood refractory chronic uveitis when used as first biologic modifier drug: adalimumab as starting anti-TNF-α therapy in childhood chronic uveitis, Pediatr Rheumatol Online J 11 (2013) 16, https://doi.org/10.1186/1546-0096-11-16.
[44] V. Miraldi Utz, S.T. Angeles-Han, N. Mwase, et al., Alternative biologic therapy in children failing conventional TNFα inhibitors for refractory, noninfectious, chronic anterior uveitis, Am. J. Ophthalmol. 244 (2022) 183–195, https://doi.org/10.1016/j.ajo.2022.06.024.
[45] V. Calvo-Río, M. Santos-Gómez, I. Calvo, et al., Anti-Interleukin-6 receptor tocilizumab for severe juvenile idiopathic arthritis-associated uveitis refractory to anti-tumor necrosis factor therapy: a multicenter study of twenty-five patients, Arthritis Rheumatol. 69 (2017) 668–675, https://doi.org/10.1002/art.39940.
[46] F. Burlo, C. Tumminelli, S. Pastore, et al., Subcutaneous tocilizumab in the management of non-infectious uveitis in children: a brief report, Pediatr Rheumatol Online J 21 (2023) 99, https://doi.org/10.1186/s12969-023-00883-y.
[47] C. Diener, G. Horneff, Comparison of adverse events of biologicals for treatment of juvenile idiopathic arthritis: a systematic review, Expet Opin. Drug Saf. 18 (2019) 719–732, https://doi.org/10.1080/14740338.2019.1632288.
[48] I. Maccora, M.P. dell'Anna, A. Vannacci, G. Simonini, Safety evaluations of adalimumab for childhood chronic rheumatic diseases, Expet Opin. Drug Saf. 19 (2020) 661–671, https://doi.org/10.1080/14740338.2020.1763300.
[49] J. Swart, G. Giancane, G. Horneff, et al., Pharmacovigilance in juvenile idiopathic arthritis patients treated with biologic or synthetic drugs: combined data of more than 15,000 patients from Pharmachild and national registries, Arthritis Res. Ther. 20 (2018) 285, https://doi.org/10.1186/s13075-018-1780-z.
[50] E. Miserocchi, I. Pontikaki, G. Modorati, M. Gattinara, P.L. Meroni, V. Gerloni, Anti-CD 20 monoclonal antibody (rituximab) treatment for inflammatory ocular diseases, Autoimmun. Rev. 11 (2011) 35–39, https://doi.org/10.1016/j.autrev.2011.07.001.
[51] N. Palmou-Fontana, V. Calvo-Río, J.L. Martín-Varillas, et al., Golimumab in refractory uveitis associated to juvenile idiopathic arthritis: multicentre study of 7 cases and literature review, Clin. Exp. Rheumatol. 36 (2018) 652–657.
[52] E. Miserocchi, C. Giuffrè, M. Cornalba, I. Pontikaki, R. Cimaz, JAK inhibitors in refractory juvenile idiopathic arthritis-associated uveitis, Clin. Rheumatol. 39 (2020) 847–851, https://doi.org/10.1007/s10067-019-04875-w.
[53] Oxford Centre for Evidence-Based Medicine. https://www.cebm.ox.ac.uk/resources/levels-of-evidence/oxford-centre-for-evidence-based-medicine-levels-of-evidence-march-2009.